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(54) Title: STABLE HYDRATES OF A CEPHALOSPORIN CHLORIDE SALT

(57) Abstract

The cephalosporin compound [6R, 7R]-7-[2-(2-amino-4-thiazolyl)-2-(Z)-(methoxyimino)acetamido]-3-[1-(methylamino)pyridinium-4-thiomethyl]-ceph-3-em-4-carboxylic acid chloride hydrochloride is provided as a mono-, di- or tri-hydrate. The hydrates are produced by treating an aqueous solution of the corresponding carboxylate with hydrogen chloride and have been found to possess unexpectedly superior stability properties over other forms of the compound. The hydrates may be used in the treatment and/or prevention of bacterial infections in humans and animals.

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STABLE HYDRATES OF A CEPHALOSPORIN CHLORIDE SALT

The present invention relates to a novel compound, to a process for its manufacture and to its use in the treatment and/or prevention of bacterial infections in humans and animals caused by a wide range of organisms.

EP-A-0 416 814 (Beecham Group plc) describes certain cephalosporin compounds which are described to be useful in the treatment of bacterial infections in humans and animals caused by a wide range of organisms.

One particular compound mentioned therein, ie, [6R,7R]-7-[2-(2-Amino-4-thiazolyl)-2-(Z)-(methoxyimino)acetamido]-3-[1-(methylamino)pyridinium-4-thiomethyl]-ceph-3-em-4-carboxylate (ie, example 2) has now been prepared as crystalline carboxylic acid chloride hydrochloride mono-, di- or tri-hydrate.

This particular form of the compound has unexpectedly superior stability properties over the freeze dried material of example 2 in EP-A-0416814.

Accordingly the present invention provides [6R,7R]-7-[2-(2-Amino-4-thiazolyl)-2-(Z)-(methoxyimino)acetamido]-3-[1-(methylamino)pyridinium-4-thiomethyl]-ceph-3-em-4-carboxylic acid chloride hydrochloride as a mono, di or tri-hydrate.

Preferably the present invention provides [6R,7R]-7-[2-(2-Amino-4-thiazolyl)-2-(Z)-(methoxyimino)acetamido]-3-[1-(methylamino)pyridinium-4-thiomethyl]-ceph-3-em-4-carboxylic acid chloride hydrochloride as a tri-hydrate.

The present invention further provides a process for the preparation of [6R,7R]-7-[2-(2-Amino-4-thiazolyl)-2-(Z)-(methoxyimino)acetamido]-3-[1-(methylamino)pyridinium-4-thiomethyl]-ceph-3-em-4-carboxylic acid chloride hydrochloride as a mono, di or tri-hydrate said process comprising treating an aqueous solution of [6R,7R]-7-[2-(2-Amino-4-thiazolyl)-2-(Z)-(methoxyimino)acetamido]-3-[1-(methylamino)pyridinium-4-thiomethyl]-ceph-3-em-4-carboxylate with hydrogen chloride

Suitably [6R,7R]-7-[2-(2-Amino-4-thiazolyl)-2-(Z)-(methoxyimino)acetamido]-3-[1-(methylamino)pyridinium-4-thiomethyl]-ceph-3-em-4-carboxylate is dissolved in water and treated with aqueous hydrochloric acid for example a 2 molar solution thereof. The resulting solution is suitably diluted with a water soluble organic solvent to precipitate the product; for example tetrahydrofuran. The resulting mixture may then be cooled for example overnight to 0 to 5°C, suitably at around 4°C. The resulting crystalline product may then be isolated for example by filtration, and dried for example in vacuo at ambient temperature.

It should be appreciated that more rigorous drying conditions will remove the bound molecules of water of hydration. In this way drying conditions may be conventionally controlled to give [6R,7R]-7-[2-(2-Amino-4-thiazolyl)-2-(Z)-(methoxyimino)acetamido]-3-[1-(methylamino)pyridinium-4-thiomethyl]-ceph-3-em-4-carboxylic acid chloride hydrochloride as the mono, di or tri-hydrates.

[6R,7R]-7-[2-(2-Amino-4-thiazolyl)-2-(Z)-(methoxyimino)acetamido]-3-[1-(methylamino)pyridinium-4-thiomethyl]-ceph-3-em-4-carboxylate may be prepared according to the procedures mentioned in or outlined by EP-A-416 814.

It should be appreciated that [6R,7R]-7-[2-(2-Amino-4-thiazolyl)-2-(Z)-(methoxyimino)acetamido]-3-[1-(methylamino)pyridinium-4-thiomethyl]-ceph-3-em-4-carboxylic acid chloride hydrochloride mono, di or tri-hydrate is an active medicinal product and may be formulated into unit dose forms suitable for administration to humans or animals in need of treatment.

[6R,7R]-7-[2-(2-Amino-4-thiazolyl)-2-(Z)-(methoxyimino)acetamido]-3-[1-(methylamino)pyridinium-4-thiomethyl]-ceph-3-em-4-carboxylic acid chloride hydrochloride mono, di or tri-hydrate is especially suitable for the treatment and/or prevention of bacterial diseases in animals.

Such unit dose forms may be for example those contemplated in EP-A-416 814 and those generally known in the art, especially those particularly adapted for administration to animals.

Amounts of [6R,7R]-7-[2-(2-Amino-4-thiazolyl)-2-(Z)-(methoxyimino)acetamido]-3-[1-(methylamino)pyridinium-4-thiomethyl]-ceph-3-em-4-carboxylic acid chloride hydrochloride mono, di or tri-hydrate suitable for formulation into a unit dose form and the number of unit dose forms administered to a human or animal patient is mentioned in EP-A-0 416 814 and is hereincorporated by reference.

The types of bacterial infections which may be treated by [6R,7R]-7-[2-(2-Amino-4-thiazolyl)-2-(Z)-(methoxyimino)acetamido]-3-[1-(methylamino)pyridinium-4-thiomethyl]-ceph-3-em-4-carboxylic acid chloride hydrochloride mono, di or tri-hydrate include those specifically mentioned in EP-A-416 814 which are incorporated herein by reference. Such infections are hereinafter referred to as "the infections".

The present invention therefore provides a method for the treatment and/or prevention of "the infections" which comprises administering an effective amount of [6R,7R]-7-[2-(2-Amino-4-thiazolyl)-2-(Z)-(methoxyimino)acetamido]-3-[1-(methylamino)pyridinium-4-thiomethyl]-ceph-3-em-4-carboxylic acid chloride hydrochloride mono, di or tri-hydrate to a sufferer in need thereof.

The present invention also provides the use of [6R,7R]-7-[2-(2-Amino-4-thiazolyl)-2-(Z)-(methoxyimino)acetamido]-3-[1-(methylamino)pyridinium-4-thiomethyl]-ceph-3-em-4-carboxylic acid chloride hydrochloride mono, di or tri-hydrate in the treatment and/or prevention of "the infections" in humans or animals.

The present invention also provides the use of [6R,7R]-7-[2-(2-Amino-4-thiazolyl)-2-(Z)-(methoxyimino)acetamido]-3-[1-(methylamino)pyridinium-4-thiomethyl]-ceph-3-em-4-carboxylic acid chloride hydrochloride mono, di or tri-hydrate in the manufacture of a medicament for treating and/or preventing "the infections" in humans or animals.

The present invention also provides a pharmaceutical composition for use in the treatment and/or prevention of "the infections" in animals or humans which comprises admixing [6R,7R]-7-[2-(2-Amino-4-thiazolyl)-2-(Z)-(methoxyimino)acetamido]-3-[1-(methylamino)pyridinium-4-thiomethyl]-ceph-3-em-4-carboxylic acid chloride hydrochloride mono, di or tri-hydrate with pharmaceutically acceptable excipients.

The following example illustrates the present invention.

Example 1

[6R,7R]-7-[2-(2-Amino-4-thiazolyl)-2-(Z)-(methoxyimino)acetamido]-3-[1-(methylamino)pyridinium-4-thiomethyl]-ceph-3-em-4-carboxylic acid chloride hydrochloride trihydrate

[6R,7R]-7-[2-(2-Amino-4-thiazolyl)-2-(Z)-(methoxyimino)acetamido]-3-[1-(methylamino)pyridinium-4-thiomethyl]-ceph-3-em-4-carboxylate (2.75g, 5.1mmol) was dissolved in H_20 (10mL) and acidified with 2M aqueous HCl (15mL). The solution was diluted with THF (400mL) and the mixture stored at 4°C overnight. The resulting crystalline material was collected by filtration, washed with THF (100mL) and dried *in vacuo* at 20°C. The *title compound* (2.7g) was isolated as a crystalline solid (needles): δ (DMSO-d6) 2.99(s, 3H), 3.55(d,J=18Hz, 1H), 3.80(d,J=18Hz, 1H), 3.95(s, 3H), 4.41(q, J=12.9Hz, 2H), 5.24(d, J=4.8Hz, 1H), 5.79(d.d, J=7.9Hz, 4.8Hz, 1H), 6.96(s, 1H), 8.01(d, J=7.3Hz, 2H), 8.92(d, J=7.2Hz, 2H), 9.87(d, J=7.9Hz, 1H); H_20 8.9% (Theory 8.16%).

CLAIMS

1. [6R, 7R]-7-[2-(2-Amino-4-thiazolyl)-2-(Z)-(methoxyimino)acetamido]-3-[1-(methylamino)pyridinium-4-thiomethyl]-ceph-3-em-4-carboxylic acid chloride hydrochloride as a mono-, di-, or tri- hydrate.

2. [6R, 7R]-7-[2-(2-Amino-4-thiazolyl)-2-(Z)-(methoxyimino)acetamido]-3-[1-(methylamino)pyridinium-4-thiomethyl]-ceph-3-em-4-carboxylic acid chloride hydrochloride as a tri-hydrate.

3. A process for the preparation of [6R, 7R]-7-[2-(2-amino-4-thiazolyl)-2-(Z)-(methoxyimino)acetamido]-3-[1-(methylamino)pyridinium-4-thiomethyl]-ceph-3-em-4-carboxylic acid chloride hydrochloride as a mono-, di or tri-hydrate, said process comprising treating an aqueous solution of [6R, 7R]-7-[2-(2-amino-4-thiazolyl)-2-(Z)-(methoxyimino)acetamido]-3-[1-(methylamino) pyridinium-4-thiomethyl]-ceph-3-em-4-carboxylate with hydrogen chloride.

4. The use of [6R, 7R]-7-[2-(2-amino-4-thiazolyl)-2-(Z)-(methoxyimino) acetamido]-3-[1-(methylamino)pyridinium-4-thiomethyl]-ceph-3-em-4-carboxylic acid chloride hydrochloride mono-, di- or tri-hydrate in the manufacture of a medicament for treating and/or preventing bacterial infections in humans or animals.

5. A pharmaceutical composition for use in the treatment and/or prevention of bacterial infections in humans or animals which comprises an admixture of [6R, 7R]-7-[2-(2-amino-4-thiazolyl)-2-(Z)-(methoxyimino) acetamido]-3-[1-(methylamino)pyridinium-4-thiomethyl]-ceph-3-em-4-carboxylic acid chloride hydrochloride mono-, di- or tri-hydrate with pharmaceutically acceptable excipients.

6. A method for the treatment and/or prevention of bacterial infections in humans or animals which comprises administering an effective amount of [6R, 7R]-7-[2-(2-amino-4-thiazolyl)-2-(Z)-(methoxyimino)acetamido]-3-[1-(methylamino)pyridinium-4-thiomethyl]-ceph-3-em-4-carboxylic acid chloride hydrochloride mono-, di- or tri-hydrate to a sufferer in need thereof.

7. The use of [6R, 7R]-7-[2-(2-amino-4-thiazolyl)-2-(Z)-(methoxyimino) acetamido]-3-[1-(methylamino)pyridinium-4-thiomethyl]-ceph-3-em-4-carboxylic acid chloride hydrochloride mono-, di- or tri-hydrate in the treatment and/or prevention of bacterial infections in humans or animals.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D501/36 A61K31/545

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 416 814 (BEECHAM GROUP PLC) 13 March 1991 cited in the application see example 54, page 68	1-7
A	EP,A,0 638 573 (LUCKY LTD) 15 February 1995 see the whole document	1-7
A	US,A,4 146 710 (NAITO KENZO ET AL) 27 March 1979 see the whole document	1-7

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Information on patent family members

Int ional Application No
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